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Short Communication

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Is Fetal Karyotyping A Significant Tool in Evaluation of Recurrent Pregnancy Loss?

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Abstract

Karyotyping is a technique to examine the chromosomes-abnormality or structural defects. Karyotyping can be used to detect a variety of genetic disorders. For example, a woman who has premature ovarian failure may have a chromosomal defect that karyotyping can pinpoint. In a developing country like India where cost dictates the patient courses of action it is up to government funded hospitals to make judicious decisions and make use of this technology.

Keywords: Fetal Karyotyping, fetal screening.

Introduction

Recurrent pregnancy loss is truly a trying time for the patient and her family. The objective of work up of such patient is to ascertain the medical history, get relevant investigations to reach to the cause which gives the insight into giving relevant information to the patient about the prognosis and effective treatment based on the parameters evaluated. Sixty percent of miscarriages have chromosomal aberrations as the underlying cause [1-3]. In a study by Carp et al., trisomy's were the most common form of aberration, occurring in 66.7 % of chromosomally aberrant embryos, with trisomies 21,16 and 18 being the most common [4]. The standard banding technique for karyotyping can only assess structural and numerical rearrangements, and is liable to fail due to contamination, culture failure, overgrowth of maternal cells. Other more sophisticated tests such as comparative genomic hybridization (CGH) or multiplex fluorescence in situ hybridization (M-FISH), may overcome this problem and give additional information such as uniparental disomy or skewed X chromosome inactivation [5].

Favor of Karyotyping

Karyotyping of the abortus gives prognostic information regarding subsequent pregnancy outcomes. A study by Warburton et al., concluded that after a previous trisomic miscarriage, the prognosis is favorable [6]. Another study by Ogasawara et al., showed there was a statistically significant trend for a patient with an aneuploidy abortion to have a better prognosis [5]. In women with three miscarriages and an aneuploidy miscarriage, reassurance of a good prognosis may be sufficient and may save the patient more extensive investigation and treatment. This may not be in euploidic abortions. The aneuploidy abortion is due to fetal cause and so better chances of euploid fetus subsequently. However, a euploid abortus indicates that the cause of miscarriage is mostly due to maternal, the problem is likely to recur in next pregnancy, thus worsening the prognosis. In a study by Sullivan et al., 15% of aneuploidy abortions were followed by subsequent aneuploidy abortion and that 85 % can be assured of good prognosis [4]. Fetal karyotyping also directs treatment. If the fetus is karyotypically abnormal, a normal embryo can be provided to the mother by PGS. While in cases the fetus is normal, the maternal environment needs to be addressed. In addition, in cases of possibility of fetal chromosomal aberrations, PGS is done to provide the patient with a chromosomally normal embryo. Thus, PGS has a role in repeated aneuploidy, or in older patients. In case of elderly with recurrent pregnancy loss, fetal karyotyping could actually be a guide to her treatment. If the abortus karyotype in such cases is aneuploidic, she could be counseled to go for ovum donation on account of increasing age. If fetal karyotyping had not been performed, she would have been recommended paternal leukocyte immunization or immunoglobulin in view of her advanced age resulting in poor prognosis.

There is no substitute for karyotyping the abortus – two techniques have been attempted: Karyotyping of the parents and PGS as a diagnostic procedure. Chromosomal aberrations are often suspected to have a recurring basis due to either a structural anomaly such as reciprocal or robertsonian translocation; or mosaicism for numerical aberrations. However, parental karyotyping does not provide a diagnosis or prognosis, nor does it direct treatment.

Table 1: Subsequent live birth rate with parental chromosomal aberrations

	Ogasawara et al., [7]	Goddijin et al., [8]	Carp et al., [9]
Pregnancies	47	42	75
Live birth	15	30	33
Mean no of abortions	2.9	3.9	4.23

PGS is also problematic as a diagnostic and therapeutic tool when it is unknown wheather the patient losses chrmosomally normal or abnormal embryos. As it is impossible to screen all 23 chromosomes, an embryo can never be said to be normal in PGS-it can only be stated that the most common chromosomal aberrations are absent (Table-1).

Karyotyping of the abortus appears to be a single important investigation for the assessment of recurrent miscarriage. This has also been recommended by RCOG guidelines in 1998 and revised in 2003. The other methods fall short of giving insight into diagnostic, prognostic or treatment mode.

Not in Favor of Karyotyping

One of the most remarkable, and as yet unexplained, aspects of the first trimester of pregnancy is the fact that the majority (90%) of karyotypically abnormal pregnancies miscarries in the first trimester, and the majority (93%) of karyotypically normal pregnancies continues [10]. Most chromosomal abnormalities that result in spontaneous abortion are random events and are more likely to be associated with recurrent spontaneous abortion, but are uncommon even where one of the parents is a carrier (4-6% of recurrent miscarriage).

Cytogenic evaluation of sporadic spontaneous abortions show that 50-60 % of all pregnancies are chromosomally abnormal and it is well documented its due to fetal cause. The detection rates of chromosomal abnormalities have remained constant over time, independent of the culture method used or the culture success rate and have been reported to be 90 % [11-13]. The recurrence risk of another miscarriage after an aneuploidic miscarriage is not elevated or is only slightly so (16%) compared with the intial risk of all women (10-15%). Thus, routine karyotyping of fetal material in miscarriage is not thought to be worthwhile and is considered unnecessary. Half of the structural abnormalities may be inherited from a parent carrying a balanced chromosome trnslocation or inversion. This type of chromosomal abnormality can be picked up from parental karyotyping which is usually recommended after 2 or more missed abortions. As the number of miscarriage increases, the prevalence of chromosomal abnormality decreases, and the chance of recurring maternal cause increases [14].

Results of convential cytogenic analysis of spontaneous abortions depend strongly on tissue culture which has a variable failure rate. The banding technique for karyotyping can only assess structural and numerical rearrangements, and is liable to fail as a result of contamination, culture failure, or overgrowth of maternal cells. A possible disadvantage of the preparation is the discrepancy that may occur between embryonic cells and chorionic villi. Such discrepancy may be due to placental mosaicism. It has been proposed that tissue culture failure is due to genomic imbalance incompatible with normal cell proliferation. If this hypothesis is true, then the standard cytogenic analysis of spontaneous abortions may underestimate the frequency and diversity of detected chromosomal abnormalities. Thus, the fetal karyotype may not be represented correctly by the villous karyotype. More sophisticated tests such ascomparative genomic hybridization (CGH) or multiplex flouescence in situ hybridization (M-FISH) may overcome this problem and give additional information on uniparental disomy or skewed x- chromosome inactivation. FISH Or CGH techniques have not significantly changed the clinical approach or the psychological benefit, have high cost and require sophisticated laboratory requirements.

Consensus remarks

American College of Obstetricians and Gynecologists (ACOG) [15]

"Many experts obtain a karyotype of the abortus tissue when a couple with recurrent pregnancy loss experiences a subsequent spontaneous abortion. The rationale is that if the abortus is aneuploid, the physician may conclude that a maternal cause of pregnancy loss is excluded. Also an abnormal abortus karyotype is a legitimate explanation for the loss that may provide a source of comfort to the couple. "However, no published evidence supports this hypothesis, and definite recommendations for routinely obtaining abortus karyotyping cannot be made.

American College of Obstetricians and Gynecologists (ACOG) [16]

"If the karyotype of the miscarriage pregnancy is abnormal, there is a better prognosis in the next pregnancy. Cytogenic testing is an expensive tool and may be resrved for patients who have undergone treatment in the index pregnancy. For them karyotyping of the products of conception provides useful information for counseling and future management. This statement is under Category C-level IV-which is based solely on expert opinion with no valid clinical studies.

Joint Working Party of Royal College of Pathologist and Royal College of Gynecologists [17]

'Because of high failure rate of post abortal and post stillbirth karyotyping, the working party recommends that multiple samples be collected, usually placenta and full thickness skin. Consideration should be given to collecting a specimen in utero before the termination process begins

The consensus opinion of gynecologists, obstetrician and fertility specialists from 19 countries state that improved techniques in cytogenics have permitted more accurate and reliable assessment of the product of conception. Given these improvements in our diagnostic ability, it is even more important that every effort be made to study the products of conception in every case of miscarriage in therapeutic trials so that a more valid evaluation can be made regarding the efficacy of the experimental treatment. They do not recommend karyotyping of abortus material.

Conclusion

Since no clear cut guidelines to recommend or negate the use of karyotyping of fetal products in recurrent pregnancy loss. Selective Karyotyping may be used in the diagnostic work up of couples with recurrent pregnancy loss in high risk cases. In general, large gap exists between evidence based medicine and daily clinical practice, and gynaecologists may judiciously suse this method to solve the complexities and get a breakthrough in cases of recurrent pregnancy loss.

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